Obscure Causes of Dyspnea

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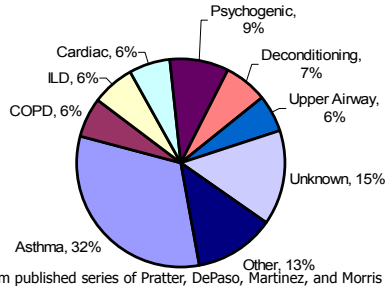
Goals of Presentation

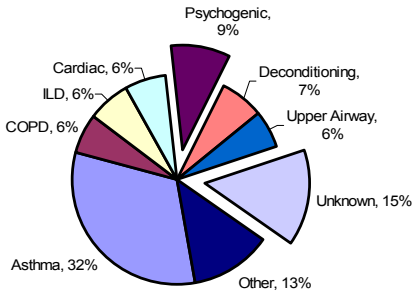
- The language of dyspnea
- The evaluation of dyspnea
- Obscure causes of dyspnea and their characteristic presentations

Causes of Undiagnosed Dyspnea in Pulmonary Clinics (n = 306)



From published series of Pratter, DePaso, Martinez, and Morris

Causes of Undiagnosed Dyspnea in Pulmonary Clinics (n = 306)



Evaluation of Dyspnea – Step 1

- History
- Physical Examination
- Spirometry, Pulse Oximetry
- Chest Radiograph
- EKG
- Lab: CBC, Thyroid Function, Electrolytes and Hepatic and Renal Function

Adapted from Niven, Weisman, Mahler Odonnell: Dyspnea: Mechanisms, Measurement and Management, 2nd ed, 2005

Evaluation of Dyspnea – Step 2 Focused Testing

- Echocardiogram
- Complete PFTs (Dco, Lung volumes, Flow-volume loops, Resp. pressures, ABG)
- Stress Echo / Thallium

Adapted from Niven, Weisman, Mahler O'Donnell: Dyspnea: Mechanisms, Measurement and Management, 2nd ed, 2005

Evaluation of Dyspnea – Step 2 Focused Testing - Continued

- Bronchoprovocation (Methacholine)
- Upper airway inspection
- High Resolution Chest CT
- CT Angio, V/Q scan
- Ambulatory Esophageal pH probe
- Cardiopulmonary Exercise Testing

Dyspnea Evaluation – Step 3 Advanced Testing

- Cardiac Catheterization
- Muscle Biopsy
- Lung Biopsy

Adapted from Niven, Weisman, Mahler O'Donnell: Dyspnea: Mechanisms, Measurement and Management, 2nd ed, 2005

The Language of Dyspnea 1.

- Asthma – Chest Tightness, Wheeziness
- Severe Asthma – Increased work to breathe
- COPD – Increased effort to take in breath
- Restrictive Lung Diseases –shallow, rapid breathing

•Simon PM, Schwartzstein RM, Weiss JW, Fencl V, Teghtsoonian M, Weinberger SE. Distinguishable types of dyspnea in patients with shortness of breath. Am Rev Respir Dis. 1990;142:1009-14
•Mahler DA, Harver A, Lentine T, Scott JA, Beck K, Schwartzstein RM. Descriptors of breathlessness in cardiorespiratory diseases.Am J Respir Crit Care Med. 1996;154:1357-63

The Language of Dyspnea 2.

- CHF – Not enough oxygen in the air, "bad air", air hunger
- Low Cardiac Output – General fatigue, weakness, light-headed
- Hypoxia – Non-specific ill-feeling, rapid breathing, anxiety

Atypical Presentations of Asthma

- Occupational
- Exercise-induced
- Aspirin-associated
- Obscure allergen
- Reactive Airway Disease Syndrome (RADS)
- Vocal Cord Dysfunction

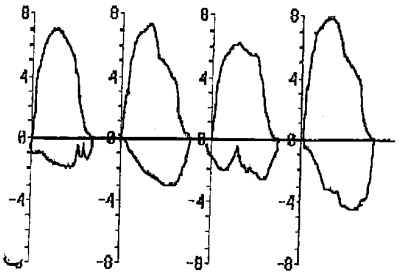
Asthma-like Syndromes 1

- Reactive Airway Disease Syndrome (RADS)
  - Occurs after toxic irritant exposure
  - May have initial acute dyspnea, ALI
  - Develop sensitivity to irritants or strong odors
  - Methacholine test usually positive
  - Inhaled corticosteroids of uncertain benefit
  - Anticholinergic bronchodilators recommended
  - Recovery usual over several years

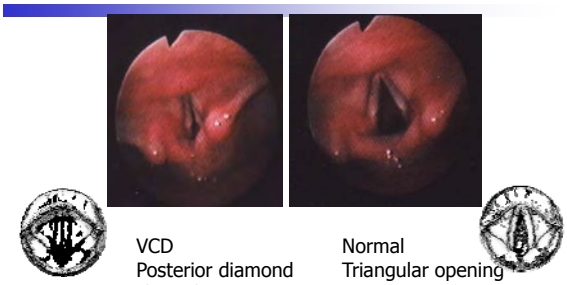
Vocal Cord Dysfunction Syndrome

- Mimics or may co-exist with asthma
- Sudden onset
- Cannot speak during attack
- Commonly associated with panic attack
- Rarely awakens patient at night
- More common in women, health care workers

Flow-Volume Loops Show Irregular Inspiratory Limbs



Inspiration in VCD - Laryngoscopy



VCD
Posterior diamond shaped aperture

Normal
Triangular opening

Vocal Cord Dysfunction – Clinical Characteristics

	VCD (n = 42)	VCD +Asthma (n = 53)	Asthma (n = 42)
Age	34.3*	42.6	43.0
M/F	1/41*	14/39	11/31
W/B	40/2	47/6	40/2
Pk-yrs	1.29	17.5	4.9
% ideal Wt	139%	134%	131%
Med occup	10/35	7/37	7/41

Newman et al. AJRCCM 1995, 152:1382

Vocal Cord Dysfunction - Treatment

- Speech therapy
- Biofeedback
- Avoidance of irritant triggers
- Treatment of co-morbid asthma and psychiatric disorders

Exercise-induced Vocal Cord Dysfunction

- Difficult to diagnose
  - Occurs in elite athletes / fit amateurs
  - Symptoms are typically highly reproducible
- Cardiopulmonary Exercise Testing w/ Flow-volume loops recorded during and after exercise

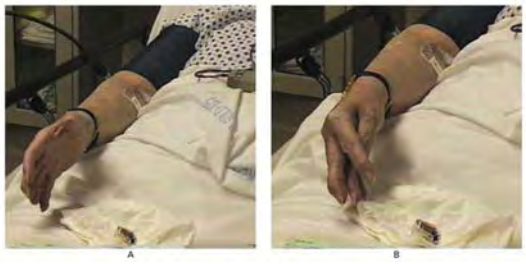
Hyperventilation Syndrome – Panic Attacks

- Most common cause of acute dyspnea in some ED series, 25% of patients in vertigo clinic, 5-10% of primary care patients
- Breathing pattern is usually slow and deep, not rapid
- Alkalemic symptoms
  - Paresthesias of hands, face, mouth, scalp
  - Light-headedness, "giddy"
  - Chest pressure, tightness
- Panic Sensation

Hyperventilation Syndrome – Diagnosis and Treatment

- Arterial blood gas during attack shows acute respiratory acidosis
- Hypocalcemia with tetany (Trousseau's sign) and Q-T prolongation in severe cases
- Symptoms can be reproduced by voluntary hyperventilation
- Reassurance and cognitive therapy often helpful.

Trousseau's Sign



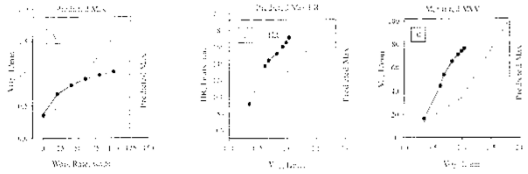
Exercise-induced hyperventilation

- Characteristic CPET study
  - High V_E/VO_2 and
  - High V_E/VCO_2
  - Low end-tidal CO_2
- Usually considered psychogenic

Exercise Hyperventilation and Mitochondrial Myopathy

- Occurs in ~8.5% of difficult to diagnose dyspnea
- Myopathy symptoms may be subtle
- Elevated ventilatory response and heart-rate response to exercise may be diagnosed as psychogenic or de-conditioning

CP Exercise Test with Mitochondrial Myopathy



Low VO2max, High Heart Rate Response, High Ventilatory Response

Flaherty KR, Wald J, Weisman IM, Zeballos RJ, Schork MA, Blaivas M, Rubenfire M, Martinez FJ. Unexplained exertional limitation: characterization of patients with a mitochondrial myopathy. Am J Respir Crit Care Med. 2001

Functional or "Sighing" Dyspnea

- Possibly most common cause of undiagnosed dyspnea in pulmonary clinic
- Little is written about it
- Generally healthy adult with normal PFTs, CXR, Cardiac evaluation
- Characteristic History and Examination

Functional or Sighing Dyspnea 2

- Episodic sense of inability to fully expand lungs
  - "I take a breath but it doesn't feel like I could fully expand my lungs." "Chest feels tight."
- Occurs at rest, often relieved by exercise or other distraction
- Usually not provoked by stress or anxiety but may cause anxiety
- "Sighing" pattern of respiration during episode
- May be confused with asthma

Functional or Sighing Dyspnea 3

- Prognosis is benign
- Condition will wax and wane, but often chronic
- Reassurance is usually adequate, may need to use distraction methods such as isometric exercises
- Anxiolytics and narcotics have been used but usually not helpful

Bilateral Diaphragmatic Weakness

- Causes severe orthopnea, sudden onset
- Hypoinflation on CXR
- Diagnosis is usually delayed 2 years
- Diagnosis is suggested by inspiratory pressure < 20 cm + Fall in VC in supine posture > 20%
- Confirmation by Pdi or EMGdi

Unilateral Diaphragm Paralysis (Parsonage-Turner Syndrome, Brachial Amyotrophy)

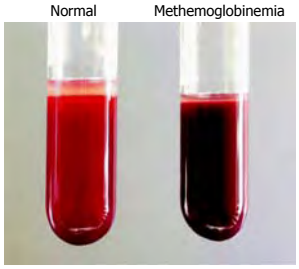
- Often starts with viral syndrome
- Severe neck and shoulder pain, often diagnosed as myalgias, bursitis or cervical radiculopathy
- Onset of exertional dyspnea days to week later
- Hemidiaphragm elevation on CXR
- Diagnosis by characteristic EMG
- Spontaneous recovery in 75% cases

Methemoglobinemia

- Functional anemia, may be fatal
- Dyspnea with functional hemoglobin less than 8 gm/dl
- Pulse Oximeter Reads ~88% and is inconsistent with ABG calculated saturation
- Most commonly caused by dapsone, primaquine, benzocaine

Oxygenated blood is chocolate brown

Normal Methemoglobinemia



Ash-Bernal et al. Acquired methemoglobinemia: a retrospective series of 138 cases at 2 teaching hospitals. Medicine 83:265 (2004)

Causes of Methemoglobinemia

Etiology or Context of MetHgb in 138 patients

Cause	Total Cases	Mean MetHgb
Dapsone	58	7.60%
Surgery/ anesthesia	32	3.30%
Unknown	24	4.10%
Dehydration (Pediatric)	6	28.00%
20% Benzocaine	5	43.80%
Primaquine	5	6.20%
Dapsone + Primaquine	4	16.50%
Other	4	7.20%

Ash-Bernal et al. Acquired methemoglobinemia: a retrospective series of 138 cases at 2 teaching hospitals. Medicine 83:265 (2004)

Platypnea-Orthodeoxia Syndromes

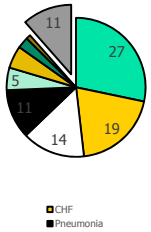
- Hepatopulmonary syndrome with cirrhosis
- Pulmonary AVM at lung base
- Atrial Septal Defect
- Left Atrial Myxoma

Platypnea without orthodeoxia

- Dysautonomia
- Orthostatic Hypotension

Dyspnea with Clopidogrel (Plavix) – 11% unexplained

- Dyspnea in 4.2% of patients s/p stent with Clopidogrel/ASA (n = 3719)
  - COPD – 27%
  - CHF – 19%
  - Cancer 14%
  - Pneumonia – 11%
  - PHT – 5%
  - Pericarditis – 5%
  - Arrhythmias 2.5%
  - Other causes – 1%
  - Unexplained 11%



Serebruany V et al. Incidence and causes of new-onset dyspnea in 3,719 patients treated with clopidogrel and aspirincombination after coronary stenting. Thromb Haemost: 2008;100(2):314-8

Current Controversies © Schattauer 2012

Why does ticagrelor induce dyspnea? (Brilinta™)

Marco Cattaneo; Elena M. Faioni

Thromb Haemost 2012; 108: 1031–1036

- Dyspnea occurs in 10-38%
- No change in Pulmonary, cardiac function
- Hypothesized causes: increased adenosine levels or $P2Y_{12}$ Blockade
- Usually diminishes over days

Other Causes

- Hyperventilation Syndrome
- Metabolic Acidosis
  - RTA, DKA, Diamox
- Pulmonary Vascular Disease
  - PHT
  - PE
  - Factor V Leiden homozygous form
- Obesity
- GERD, Recurrent aspiration, Zenker's
- Upper Airway Obstruction

Conclusions

- Many obscure causes of dyspnea can be diagnosed based on clinical presentation
- Careful review of the history can give important clues to the diagnosis and direct specific diagnostic testing

Cases for discussion

- 62 y/o F4 Judge with exertional dyspnea, Dx
- 60 y/o F homemaker with exertional dyspnea, Dx
- 18 y/o F athlete with exertional dyspnea, Dx
- 59 y/o M with ESRD on dialysis

DePaso WJ, Winterbauer RH, Lusk JA, Springmeyer SC. Chronic dyspnea unexplained by history, physical examination, chest roentgenogram, and spirometry: analysis of a seven year experience. Chest 1991; 100: 1293-1299.

Pratter MR, Curley FJ, Dubois J, Irwin RS. Cause and evaluation of chronic dyspnea in a pulmonary disease clinic. Arch Intern Med 1989; 149: 2277-2282.

Martinez FJ, Stanopoulos I, Acero R, Becker FS, Pickering R, Beamis JF. Graded comprehensive cardiopulmonary exercise testing in the evaluation of dyspnea unexplained by routine evaluation. Chest 1994; 105: 168-174.

THE JOURNAL OF FAMILY PRACTICE

Sigh syndrome: Is it a sign of trouble?

Sigh syndrome, which involves irrepressible, persistent sighing, may be stressful for the patient, but it's benign

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Practice recommendation

- Sigh syndrome is a genuine medical diagnosis with distinct criteria, conferring significant stress for those affected. Despite outward signs of an abnormal breathing pattern, this symptomatology is unrelated to any respiratory or organic pathology.
- Ancillary testing and medication seem unnecessary; supporting reassurance appears sufficient, since the syndrome has a favorable outcome.

Abstract

Objective The goal of this study was to identify the characteristics and clinical course of patients presenting with considerable stress regarding irrepressible persistent sighing, and to determine whether any association exists between this syndrome and respiratory or other organic disease during the acute or follow-up period.

Study design We conducted a case series review of patients diagnosed with a defined symptom complex and gathered relevant data.

Population Forty patients who presented to 3 clinics in Israel met our 10 criteria for sigh syndrome: recurrent sighing (at least once a minute, for varying lengths of time throughout the day); otherwise shallow respiration; patient conviction that deep breaths are obstructed; intensity of episodes provokes stress leading to consultation; no obvious trigger; episodes last a few days to several weeks; no interference with speech; sighing is absent during sleep; no correlation with physical activity or rest; and self-limited.

Outcomes measured We assessed demographic and health status information, as well as recent circumstances that could have served as triggers for the symptoms. We also performed systematic diagnoses of acute and chronic organic disease.

Results Physicians diagnosed "sigh syndrome" in 40 subjects (19 men [47.5%]), mean age 31.8 years, during the 3-year study period. All patients conformed to 10 sigh syndrome criteria. In 13 patients (32.5%), a significant traumatic event preceded onset of symptoms. Ten (25%) had previous anxiety or somatoform-related disorders. For 23 patients (57.5%), the sigh syndrome episode repeated itself after an initial episode. We found no association in any of the cases with any form of organic disease. Likewise, during the follow-up period (on average, 18 months), we did not observe the development of a specific organic disorder in any case.

Conclusions The "sigh syndrome" runs a benign course; it mainly demands the support and understanding of the treating physician to allay any patient concerns.

CONTINUED

IN THIS ARTICLE

THE JOURNAL OF FAMILY PRACTICE

In our clinical practices, we have repeatedly cared for patients who came into our clinics because of a worrisome irregular breathing pattern characterized by a deep inspiration, and followed by a noisy expiration. We have referred to the set of clinical signs that these patients present with as "sigh syndrome."

We have long suspected that sigh syndrome is an underdiagnosed and self-limited condition that is often mistaken for a serious respiratory disorder. In our experience, this syndrome runs a benign course. However, we believed that this syndrome had characteristic and consistent features, and should not be considered a diagnosis of exclusion.

Thus, we undertook a study to observe a group of subjects with these features to judge whether this subjectively alarming symptom complex is in fact harmless, and whether it is appropriate to respond to it as we had, by taking a stress-alleviating approach alone.

What is sigh syndrome?

Patients with sigh syndrome exhibit a compulsion to perform single but repeated deep inspirations, accompanied by a sensation of difficulty in inhaling a sufficient quantity of air. Each inspiration is followed by a prolonged, sometimes noisy expiration—namely, a sigh. Observing such abnormal breaths and confirming that the patient feels a concomitant inability to fill his lungs to capacity is sufficient to make the diagnosis.

This breathing compulsion is irregular in nature: It may occur once a minute or several times a minute, and this breathing pattern may continue—on and off throughout the day—for a few days to several weeks. In our experience, it provokes significant anxiety in patients, prompting them to seek medical advice. It does not occur when the patient is asleep, and it is not triggered by physical activity.

Both patient and doctor may, at first, be convinced that the problem reflects a serious illness. The 10 features of sigh syndrome (**TABLE 1**) constitute a proposed definition. All of our study subjects exhibited these 10 features.

FAST TRACK

In 13 of the 40 cases of sigh syndrome, the patient had experienced a recent, significant traumatic event

Sighing as an illness marker

Sighing has been described as one member of a group of signs exhibited by depressed or anxiety-ridden patients.[1] While Perin et al[2] were the first to point out the importance of distinguishing between sighing and respiratory disease, sighing per se has never been identified as a discrete illness marker.

A number of psychiatric disorders are already well known to incorporate breathing and chest symptoms along with widespread somatization. These include globus hystericus, neurocirculatory asthenia, and Tietze syndrome.[3–6] As such, the acute pain of precordial catch syndrome stands out as an example of a distinguishable, clear-cut clinical state devoid of any apparent organic basis.[7,8]

Methods

How we recruited the patients

Data was collected from 3 family practice clinics in Israel from February 2002 to February 2005. We requested that these practices contribute data of consecutive clinical cases presenting with the 10 set symptoms of sigh syndrome (**TABLE 1**).

Data collected included basic demographics, the circumstances of the onset of symptoms, concurrent medical conditions, and any associated symptoms. We assessed the patients' education level by asking questions pertaining to their years of schooling and college degrees. Patients rated their own economic status as being below, average, or above-average income.

The main outcome we examined was the clinical course of the sighing episodes during the ensuing months after their visit, in order to determine whether any patients developed a form of significant organic disease or a disorder that led to hospitalization.

Results

40 cases that cut across the socioeconomic spectrum

Forty patients were recruited for this study. Nineteen (47.5%) were male; their ages ranged from 7 to 53 (mean, 31.8; standard deviation, 13.7). Two patients (5%) were Ashkenazi Jews; 34 (85%) were of North African ethnicity (Sephardic Jews); the other 4 were of varied Asian and European ethnicity. The number of patients with North African ethnicity overrepresents that of the population in their communities. Additionally, 3 members of this group were from the same family.

There was no predilection toward any specific education level or socioeconomic status. The occupations of the subjects were diverse.

TABLE 1

10 features of sigh syndrome

1. **Recurrent, forced deep inspiration** (one or more times per minute, continuing for varying lengths of time throughout the day), followed by a prolonged and often audible **sigh**
2. Otherwise **shallow respiration**
3. Patient believes that **each deep breath is obstructed in some way**
4. Intensity of episodes provokes **ample stress,** leading the patient to seek medical attention
5. **Spontaneous episodes;** usually **no obvious trigger** or provocation
6. Episodes last **a few days to several weeks**
7. **No interference with speech;** conversation is normal between the deep breaths and sighs
8. **Sighing is absent during sleep**
9. **There is no correlation with physical activity** or rest
10. **Self-limited;** responds well to reassurance.

Their clinical characteristics

The clinical characteristics of the 40 patients are presented in **TABLE 2**. The subjects' sighing began at various times of the day, without relationship to eating or any other activity, and disappeared during sleep. All patients reported the same feeling: that of an extra effort demanded to perform full inspiration. In many cases, adult patients were certain their complaints were a sign of cardiac or respiratory disease, and they were very concerned that there was some grave, underlying disorder.

History and examination failed to reveal evidence of any somatic findings related to breathing difficulty. Breathing rate was within normal limits in all cases.

The physicians' initial encounters with these patients led to further examination in many cases: electrocardiography, blood oxygen saturation, and complete blood counts. However, no abnormalities were found on any of these tests. Medications, if prescribed at all during these consultations, were usually given to alleviate insomnia or anxiety. Further ancillary investigations or referrals were not ordered.

The sole notable finding on physical examination was a typical murmur (which had already been diagnosed) in a young girl with a congenital atrial septal defect. This 7-year-old developed repeated episodes of sigh syndrome just before her annual visit to the pediatric cardiologist; her mother believed that the child was frightened by the thought of possible future surgery.

Traumatic events, anxiety disorders suggest stress as a cause

Thirteen patient histories disclosed a definite, recent, significant traumatic event that may have triggered the onset of sigh syndrome. Examples of 2 triggering events are the terrorist murder of several members of a neighbor's family, and a near-miss with a mortar shell. One subject—a teenager—had recently been left alone in the dark with 2 younger siblings during a power blackout; another young woman said that the sighing episodes began when she decided to get married.

Ten patients had previously diagnosed neurotic disorders, mainly generalized anxiety; these included 2 cases of somatization disorder and 1 case of posttraumatic stress disorder. This information from the patients' histories was documented in their medical files.

CONTINUED

FAST TRACK

The clustering of the syndrome in North African patients—and in one family—suggests that sigh syndrome may be a cultural or adopted expression of uneasiness

TABLE 2

Clinical characteristics of the 40 patients studied—One third experienced a traumatic event

CHARACTERISTIC	YES	NO
Smoker	2 (5%)	38 (95%)
History of anxiety or somatoform disorder	10 (25%)	30 (75%)
Taking prescription medication at time of diagnosis	4 (10%)	36 (90%)
Recurrence of sighing episodes during follow-up period	24 (60%)	16 (40%)
Trigger event (eg, exposure to traumatic event 1 month before presentation with syndrome)	13 (32.5%)	27 (67.5%)

FAST TRACK

Emphasize to your patient with sigh syndrome that further treatment is unnecessary

Episodes appear to be self-limited

In all patients, the episodes were self-limited. During the follow-up period, lasting an average of 18 months, none of the patients showed additional medical conditions—respiratory or otherwise—that could be linked to episodes of sigh syndrome. Recurrences of sighing episodes were reported by 24 subjects (60%) after the marker episode. One patient was diagnosed with carcinoma of the pancreas 2 years into follow-up, and later died.

Discussion

A benign, transient disorder

Aside from the solitary and unrelated death noted above, examination and follow-up in all 40 cases did not lead to an alternative diagnosis. Sigh syndrome thus seems to be an entirely benign and transient condition with no sequelae aside from possible recurrences.

Although the pathophysiology is unclear, our finding that 32.5% of patients had a recent traumatic incident strongly suggests a stress-related condition. Furthermore, 25% of the patients were already known to suffer from intermittent anxiety or somatoform disorders, although none were taking medications for these conditions. This adds support to the assumption that a mind-body interaction is underpinning the disorder. Large-scale migration, recent war or terrorist acts, or natural disaster are likely to increase the chances that the average physician will see a patient with sigh syndrome.

A tendency towards North African/Sephardic ethnicity, rather than European ethnicity—in addition to the cluster of 3 cases belonging to the same family—suggests the presentation may be a subconscious cultural, learned, or adopted expression of uneasiness.

Making your evaluation: History and physical are enough

The diagnostic evaluation of sigh syndrome—consisting of careful history-taking and a thorough physical examination—should be sufficient to differentiate it from an array of organic diseases. A physical examination is imperative to exclude other causes for this breathing abnormality.

Ancillary testing is rarely, if ever, indicated. It can perhaps be justified only if the condition is accompanied by an additional (if serendipitous) finding such as the cardiac murmur in the 7-year-old girl noted earlier. Physicians sometimes perform unnecessary investigations, being reluctant to base their diagnoses solely on their clinical expertise.[9] A patient may interpret this testing as uncertainty or begin to doubt the diagnosis, thus augmenting—rather than reducing—any anxiety.[10] The additional burden of the costs and possible side effects compound the futility of testing indiscriminately.[11]

Identifying these symptoms with the name "sigh syndrome," and basing this diagnosis on the history and physical examination, stresses certainty and familiarity with the diagnosis.[9] Not only does this reassure the patient, but it eases communication between professionals and forms a basis for research.

Management: Reassure your patient

Management of sigh syndrome consists largely of providing reassurances to your patient. You should emphasize that the condition is real, albeit benign, and that you understand the concern it causes.

Further treatment is unnecessary, aside perhaps from addressing any associated anxiety. A self-limiting (if sometimes recurrent) course can be confidently predicted, and follow-up visits can safely be left to the patient's own discretion. Since the major correlation with sigh syndrome seems to be stress and the experience of a recent traumatic event, you should always investigate these 2 possibilities when taking the history of a patient with suspected sigh syndrome. ■

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Acknowledgments

This work was inspired and developed by Arthur Furst, MD, who died following the submission of this manuscript. Dr Furst was a distinguished and dedicated family physician, a thorough researcher, and a renowned tutor. We dedicate this article to the fond memory of a true leader in the field of rural medicine, and an exceptionally funny and amicable colleague.

Disclosure

The authors reported no potential conflict of interest relevant to this article.

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